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1. Your reference — CPW/21202

2. Patent application number *(The Patent Office will fill in this part)* — 0227342.3 — 22 NOV 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Cipla Limited
289 Bellasis Road
Mumbai Central
Mumbai 400 008
India

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — An Indian Company — 7739162001

4. Title of the invention — PHARMACEUTICAL COMPOSITION

5. Name of your agent *(if you have one)* — A A THORNTON & CO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

235 HIGH HOLBORN
LONDON WC1V 7LE

Patents ADP number *(if you know it)* — 0000075001 ✓

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application		Date of filing *(day / month / year)*
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

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b) there is an inventor who is not named as an applicant, or
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Continuation sheets of this form	
Description	9
Claim(s)	3
Abstract	1
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Request for substantive examination *(Patents Form 10/77)*	-
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11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 21.11.02

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PHARMACEUTICAL COMPOSITION

This invention relates to a pharmaceutical composition for use in the treatment of asthma and related disorders, and especially but not exclusively for the treatment of chronic obstructive pulmonary disease (COPD).

The pathophysiology of asthma and related disorders involves various distinct symptoms, including bronchoconstriction, inflammation of the airways, and increased mucous secretion, which results in wheezing, coughing and shortness of breath. A persistent or recurrent cough may exacerbate the problem by causing further irritation and inflammation of the airways. The causes of asthma are wide-ranging and not yet fully understood.

Bronchoconstriction occurs due to bronchial smooth muscle spasm and airway inflammation with mucosal edema. Asthma and other related disorders, have been known to be treated with ß-2 adrenergic receptor agonists (ß-2 agonist) as they provide a bronchodilator effect to the patients, resulting in relief from the symptoms of breathlessness. ß-2 Agonists can be short acting for immediate relief, or long acting for long-term prevention, of asthma symptoms. Short acting ß-2 agonists currently available include: salbutamol, biltolterol, pirbuterol and terbutaline. Long acting ß-2 agonists currently available include salmeterol and formoterol.

Whilst it is also known that ß-2 agonists provide symptomatic relief of bronchoconstriction in patients, another component of asthma, i.e. inflammation, often requires separate treatment. Typically this involves treatment with a steroid. Indeed, treatment with a corticosteroid is considered one of the most potent and effective therapies currently available for persistent asthma. Currently available corticosteroids include: beclomethasone, budesonide, flunisolide, fluticasone, mometasone and triamcinolone.

Bronchoconstriction and inflammation are also associated with bronchial plugging with secretions, which may be treated with anti-cholinergic agents, such as troventol, ipratropium, oxitropium and tiotropium.

These medicaments can be administered in different ways, such as in MDIs

(metered-dosage inhalers), in DPIs (dry powder inhalers), and in oral and liquid formulations. Treatment in these different ways calls for the patient to comply with different dosage regimens, different frequencies of administration, etc. Also, since most of the medications are in the form of aerosols, the patient is required to carry several formulations and dispensers, one for each of these medicaments.

To assist patient compliance, combination products are known, e.g. an inhalation combination medication of fluticasone propionate and salmeterol, the combination being provided in one easy-to-use device. This combination product provides simultaneous treatment of airway constriction by means of the ß-2 agonist (salmeterol), and treatment of inflammation by means of the steroid (fluticasone propionate).

A combination of ipratropium bromide and salbutamol is also known. This combination therapy provides an anti-cholinergic (ipratropium bromide) to reduce the bronchial secretions and a ß-2 agonist (salbutamol) to reduce constriction. Other described combinations include ipratropium and salbutamol (WO 01/76601) and tiotropium and formoterol (WO 00/47200).

It would be highly desirable, however, to provide a combination therapy suitable to reduce bronchial inflammation, bronchial constriction and bronchial secretions in a single dosage form. It would also be desirable to provide such a combination formulation in a form whereby the correct dosage of the various components is easily and safely administered.

We have now found that combination therapeutic comprising a ß-2 agonist, anti-cholinergic and a steroid or other anti-inflammatory agent surprisingly provides an enhanced, synergistic, effect in terms of treatment of bronchoconstriction, inflammation and mucous secretions of airways. Also the three-in-one combination therapy is an extremely patient-friendly combination, which results in maximum patient compliance and better control of asthma than the known combinations or single therapies.

According to one aspect of the present invention there is provided a pharmaceutical composition comprising an anticholinergic agent, a ß-2 agonist and a corticosteroid.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising separately or in combination, an anticholinergic

agent, a ß-2 agonist and a corticosteroid for simultaneous, sequential or separate administration.

One disorder which is commonly considered to be generally related to, but not the same as, asthma is chronic obstructive pulmonary disease (COPD). The treatment of this disease can present serious difficulties to the clinician. Hitherto, it has generally been treated with an anticholinergic agent, such as ipratropium, oxitropium or tiotropium, or with a combination of an anticholinergic agent and a bronchodilator (eg a combination of ipratropium and salbutamol, or of tiotropium and formoterol).

We have now found that it is highly advantageous to treat COPD with a corticosteroid and in a further aspect, the invention provides a pharmaceutical composition for the treatment of COPD which composition comprises a corticosteroid.

The invention also comprises a method of treating COPD which comprises administering a corticosteroid.

According to this aspect of the present invention, the corticosteroid can advantageously be administered together with an anticholinergic or ß-2 agonist bronchodilator, or most preferably in combination with both a ß-2 agonist and an anticholinergic. Thus, in one highly preferred embodiment of the invention, there is provided a pharmaceutical composition for the treatment of COPD, which comprises an anticholinergic agent, a ß-agonist and a corticosteroid.

The invention also includes a method of treating COPD which comprises administering an anticholinergic agent, a ß-2 agonist and a corticosteroid.

In the present invention, the anticholinergic agent is preferably ipratropium, oxitropium, or tiotropium, or a pharmaceutically acceptable derivative, eg salt or ester, thereof. Where the anticholinergic agent has stereoisomers, such as enantiomers, it may comprise one of the isomers individually, or a mixture of the isomers. The preferred anticholinergic agent is troventol or tiotropium, especially tiotropium bromide, which may be in the form of a single enantiomer, or a racemic mixture.

Preferably the ß-2 agonist is terbutaline, biltolterol, fenoterol, salbutamol, salmeterol or formoterol, or a pharmaceutically acceptable salt or ester thereof. Where the ß-2 agonist has stereoisomers, such as enantiomers, it may comprise one of the isomers individually or a mixture of the isomers.

Preferably the anti-inflammatory corticosteroid is budesonide, beclomethasone, fluticasone, flunisolide, mometasone, ciclesonide, or triamcinolone, or a pharmaceutically acceptable salt or ester thereof. Where the corticosteriod has stereoisomers, such as enantiomers, it may comprise one of the isomers individually or a mixture of the isomers.

The abovementioned compounds may exist, and be used in the present invention, in various active forms, whilst retaining the same physiological function. For example, the anticholinergic agents, ß-2 agonists and corticosteroids may exist as various acid addition salts, such as those formed from hydrochloric, hydrobromic, sulphuric, acetic, lactic, maleic, tartaric, oxalic, methanesulphonic, p-toluenesulphonic, benzenesulphonic acids. The skilled person will also appreciate that the abovementioned compounds may also exist as esters and (R) and (S) enantiomers and provided the desired activity is maintained, they may be used in the present invention.

Among the preferred triple combinations of the invention are:

(i) salmeterol, fluticasone and tiotropium;

(ii) formoterol, budesonide and tiotropium;

(iii) salmeterol, ciclesonide and tiotropium;

(iv) formoterol, budesonide and ipratropium;

(v) salmeterol, fluticasone and ipratropium;

(vi) formoterol, budesonide and oxitropium;

(vii) formoterol, ciclesonide and tiotropium; and

(viii) salbutamol, beclomethasone and ipratropium.

These preferred compositions are especially useful in the treatment of COPD. They will normally be administered by inhalation, once or twice daily. By way of example, a preferred dosage for twice daily administrations would be:

a) formoterol (6 mcg)/budesonide (200 mcg)/ipratropium (40 mcg)

b) formoterol (6 mcg)/budesonide (200 mcg)/oxitropium (200 mcg)

The pharmaceutical composition may further comprise a pharmaceutically acceptable carrier, diluent or excipient.

The pharmaceutical composition may be provided in any suitable dosage form. A preferred formulation of the composition is in the form of a suspension, a particulate suspension or a clear solution.

The pharmaceutical composition of the present invention may be administered by any suitable administration method. Preferably the composition is administered as an aerosol. The aerosol may be provided by, for example, a metered dose inhaler (MDI), dry powder inhaler (DPI), nebules, nebuliser or nasal spray.

In the case of an aerosol, the composition preferably includes a propellant, such as 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoroethane, monofluorotrichloromethane or dichlorodifluoromethane.

In the case of a particulate suspension or a solution, the composition may further comprise one or more co-solvents. The composition may comprise both a propellant and a co-solvent, in which case it is desirable that the co-solvent has a greater polarity than the propellant. The co-solvent used may be any suitable solvent. Typically the co-solvent is ethanol. Generally the ratio of propellant to solvent is between 50:50 to 99:1.

If aerosolized, the formulation may consist of a surface-active agent to stabilize the formulation and for the lubrication of a valve system in the inhaler/nebuliser/nasal spray.

Some of the most commonly used surface-active agents in the aerosol formulations are oils derived from natural sources, such as corn oil, olive oil, cotton seed oil and sunflower seed oil and phospholipids. In these embodiments, the surface-active agents are preferably used in the formulations in the ratio of 0.00002 wt% wt to 20 wt% of the active ingredients. The surface-active agents may exceed this weight ratio in cases where drug concentration in the formulation is very low.

The active ingredients in all the above aerosol formulations are preferably in the concentration of 0.001 wt% to 5 wt% of the total formulation.

The active ingredients are provided in an appropriate particle size, generally in the range from nano-size to about 12 μm. Preferably, approximately 95% are below 5 or 6 μm (micrometers), with the all particles being below 12 μm (when measured by laser), or approximately 95% below 2.5 μm and the rest of the particles between 2.5-5 μm (when measured by microscope).

According to another aspect of the invention, there is provided the use of a composition comprising an anticholinergic agent, a ß-2 agonist and a corticosteroid in the manufacture of a medicament for the prophylaxis or treatment of asthma or chronic

obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

Preferably the medicament is used for the prophylaxis or treatment of asthma or COPD.

According to another aspect of the invention there is provided a method for the prophylaxis or treatment of asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease, said method comprising administering a therapeutically effective amount of a combination of an anticholinergic agent, a ß-2 agonist and a corticosteroid, either sequentially or simultaneously, to a patient in need thereof.

According to another aspect of the invention there is provided an aerosol device, comprising a housing containing a composition as described above, and a dispensing mechanism for dispensing the composition from the housing in a metered dose.

The dispensing mechanism may include a valve capable of releasing a metered dosage of the composition. Preferably the housing is sealed and pressurized at a pressure exceeding atmospheric pressure.

The housing may be metallic, preferably aluminum. Preferably, the housing is plastic-coated, lacquer-coated or anodised. The composition of the present invention may be placed in the housing through a suitable metering device.

The invention will now be described with reference to the following examples of formulations for use in MDI's.

Example 1

	Per aerosol housing
Tiotropium bromide	2.4 mg
Salbutamol	24 mg
Budesonide	24 mg
1,1,1,2-Tetrafluoroethane	18.2 gms

Example 2

	Per aerosol housing
Tiotropium bromide	2.4 mg
Terbutaline Sulphate	60 mg
Fluticasone	12 mg
1,1,1,2-Tetrafluoroethane	18.2 gms

In the above formulations (Examples 1 and 2), the active ingredients were initially weighed in an aluminum can. Then a metering valve was placed on the can and crimped with a vacuum crimper and then the propellant HFA 134a was charged through the metering valve.

Example 3

	Per aerosol housing
Tiotropium bromide	2.4 mg
Salbutamol	24 mg
Budesonide	24 mg
Ethanol	2.73 gms
1,1,1,2-Tetrafluoroethane	15.47 gms

In the above formulation the active ingredients were first weighed in an aluminum can, then the ethanol was added and the solution was sonicated for 5 min. The metering valve was placed on the can and crimped with a vacuum crimper, and then propellant HFA 134a was charged through the metering valve.

Example 4

	Per aerosol housing
Tiotropium bromide	2.4 mg
Salbutamol	24 mg
Budesonide	24 mg
Ethanol	2.73 gms
Oleic acid (10%)	5.04 mg
1,1,1,2-Tetrafluoroethane	15.47 gms

In the above formulation the active ingredients were first weighed in an aluminum can then the ethanol and the surfactant were added and solution was sonicated for 5 min. The metering valve was placed on the can and crimped with a vacuum crimper and then the HFA 134a was charged through the metering valve.

Example 5

	Per aerosol housing
Tiotropium bromide	2.4 mg
Terbutaline Sulphate	60 mg
Fluticasone	12 mg
Ethanol	0.364 gms
1,1,1,2-Tetrafluoroethane	18.2 gms

Example 6

	Per aerosol housing
Tiotropium bromide	2.4 mg
Terbutaline Sulphate	60 mg
Fluticasone	12 mg
Ethanol	0.364 gms
Oleic acid (0.02%)	0.014 mg
1,1,1,2-Tetrafluoroethane	17.83 gms

The above formulations (Examples 5 and 6) were weighed in an aluminum can, and a metering valve was crimped on the can and the propellant added.

Example 7

A dry powder inhaler formulation was made as follows:

	mg/capsule
Formoterol Fumarate (micronised)	0.0066
Ipratropium bromide	0.048
Budesonide BP	0.1100
Lactose	qs to 25

Example 8

An inhalation solution formulation was made as follows:

	% w/v
Budesonide	0.05
Ipratropium bromide	0.025
Salbutamol sulphate	0.125
Polysorbate 80	0.1
Sodium chloride	0.9
Anhydrous citric acid	qs pH 4.5
water purified	100 ml

CLAIMS:

1 A pharmaceutical composition comprising an anticholinergic agent, a ß-2 agonist and a corticosteroid.

2 A composition according to claim 1, wherein the anticholinergic agent is troventol, ipratropium, oxitropium or tiotropium, or a pharmaceutically acceptable salt or ester thereof.

3 A composition according to claim 1 or 2, wherein the anticholinergic agent is troventol or tiotropium bromide.

4 A composition according to claim 1, 2, 3 or 4, comprising 0.001 wt% to 0.05 wt% anticholinergic agent based on the total composition.

5 A composition according to claim 1, 2, 3 or 4, wherein the ß-2 agonist is terbutaline, biltolterol, fenoterol, salbutamol, salmeterol or formoterol, or a pharmaceutically acceptable salt or ester thereof.

6 A composition according to any preceding claim, wherein the ß-2 agonist is formoterol or salmeterol or a pharmaceutically acceptable salt or ester thereof.

7 A composition according to any preceding claim, comprising 0.001 wt% to 5 wt% ß-2 agonist based on the total composition.

8 A composition according to any preceding claim, wherein the corticosteroid is budesonide, beclomethasone, fluticasone, flunisolide, mometasone, ciclesonide or triamcinolone, or a pharmaceutically acceptable salt or ester thereof.

9 A composition according to any preceding claim, wherein the corticosteroid is budesonide or fluticasone, or a pharmaceutically acceptable salt or ester thereof.

10 A composition according to any preceding claim, comprising 0.001 wt% to 5 wt% corticosteroid based on the total composition.

11 A pharmaceutical composition which comprises salmeterol, fluticasone and tiotropium.

12 A pharmaceutical composition which comprises formoterol, budesonide and tiotropium.

13 A pharmaceutical composition which comprises salmeterol, ciclesonide and tiotropium.

14 A pharmaceutical composition which comprises

a) formoterol, budesonide and ipratropium; or
b) salmeterol, fluticasone and ipratropium; or
c) formoterol, budesonide and oxitropium.
d) formoterol, ciclesonide and tiotropium.
e) salbutamol, beclomethasone and ipratropium.

15 A composition according to any preceding claim, further comprising one or more of pharmaceutically acceptable carriers, diluents and/or excipients.

16 A composition according to any preceding claim, in a form suitable for administration by inhalation.

17 A composition according to claim 16, in the form of an aerosol.

18 A composition according to claim 17, wherein the propellant is 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, monofluorotrichloromethane or dichlorodifluoromethane, or any mixture of two or more thereof.

19 A composition according to claim 17 or 18, further comprising a co-solvent.

20 A composition according to claim 19, wherein the co-solvent is ethanol.

21 A composition according to any of claims 16 to 20, further comprising a surface-active agent.

22 A composition according to claim 21, wherein the surface active agent is oleic acid or a phospholipid, or sorbitol trioleate.

23 A metered dose inhaler which contains a composition as derived in any of claims 16 to 22.

24 The use of a composition comprising an anticholinergic agent, a ß-2 agonist and a corticosteroid in the manufacture of a medicament for the prophylaxis or treatment of asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

25 A method of treating asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease, said method comprising administering a therapeutically effective amount of a combination of an anticholinergic agent, a ß-2 agonist and a corticosteroid, either sequentially or simultaneously, to a patient in need thereof.

26 An aerosol device, comprising a housing containing a composition according to any one of claims 1 to 22, and a dispensing mechanism for dispensing the composition from the housing in a metered dose.

ABSTRACT

PHARMACEUTICAL COMPOSITION

A pharmaceutical composition for the treatment of asthma comprises an anticholinergic agent, a ß-2 agonist and a corticosteroid.